Indolequinone Antitumour Agents: Correlation between Quinone Structure and Rate of Metabolism by Recombinant Human NAD(P)H: Quinone Oxidoreductase

ELECTRONIC SUPPLEMENTARY INFORMATION

Methyl 5-methoxy-1,3-dimethyl-4-nitroindole-2-carboxylate 16a

To a solution of methyl 5-methoxy-1,3-dimethylindole-2-carboxylate **15a**[1] (0.14 g, 0.6 mmol) in acetic acid (5 ml), cooled to -10 °C, was added a mixture of concentrated nitric acid (0.045 ml) and acetic acid (0.5 ml). The mixture was stirred at room temperature for 2 h. The resulting yellow suspension was poured on to an ice/water mixture and the crystals filtered off and dried. The crude product was purified by chromatography, eluting with hexane/ethyl acetate (1:1) to yield the *title compound* (0.1 g, 59%) as a yellow crystalline solid, mp 187 – 190 °C (from ethyl acetate/hexane); (Found: C, 55.9; H, 5.0; N, 9.8. $C_{13}H_{14}N_2O_5$ requires C, 56.1; H, 5.1; N, 10.1%); ν_{max} (KBr)/cm^{-1} 2991, 2950, 2852, 1696; δ_H (300 MHz; $CDCl_3$) 7.40 (1 H, d, *J* 9.2, ArH), 7.11 (1 H, d, *J* 9.2, ArH), 3.95 (6 H, s, 2 × OMe), 3.92 (3 H, s, NMe), 2.40 (3 H, s, Me); δ_C (75 MHz; $CDCl_3$) 162.8, 145.1, 134.6, 133.8, 128.1, 118.1, 116.4, 113.0 (CH), 112.1 (CH), 58.0 (Me), 51.9 (Me), 32.4 (Me), 10.0 (Me); *m/z* (EI) 278 (M^+, 97%), 261 (49), 230 (100), 229 (32), 202 (63), 201 (57), 144 (61), 77 (67).

Methyl 4-amino-5-methoxy-1,3-dimethylindole-2-carboxylate 17a

To a suspension of methyl 5-methoxy-1,3-dimethyl-4-nitroindole-2-carboxylate **16a** (0.45 g, 1.6 mmol) in ethanol (45 ml) were added tin powder (0.86 g, 7.2 mmol) and hydrochloric acid (3 M; 12 ml). The mixture was stirred at room temperature for 2 h. The solution was decanted from the excess tin, neutralized with saturated aqueous sodium hydrogen carbonate, and diluted with an equal volume of water. The mixture was extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography, eluting with hexane/ethyl acetate (4:1), to yield the *title compound* as a pale yellow solid (0.38 g, 95%), mp 70 – 71 °C (from hexane); (Found: C, 62.9; H, 6.5; N, 11.2. $C_{13}H_{16}N_2O_3$ requires C, 62.9; H, 6.5; N, 11.3%); ν_{max} (KBr)/cm^{-1} 3391, 2935, 2832, 1700, 1603; δ_H (300 MHz; $CDCl_3$) 7.03 (1 H, d, *J* 8.9, ArH), 6.64 (1 H, d, *J* 8.9, ArH), 4.36 (2 H, br s, NH_2), 3.93 (3 H, s, NMe), 3.86 (6 H, s, 2 × OMe), 2.84 (3 H, s, Me); δ_C (75 MHz; $CDCl_3$) 163.4, 139.2, 136.4, 131.6, 124.6, 119.9, 116.7, 114.2 (CH), 98.9 (CH), 58.2 (Me), 51.3 (Me), 32.2 (Me), 12.8 (Me); *m/z* (CI) 249 (MH^+, 100%), 234 (10), 219 (9), 191 (7).

Methyl 3-ethyl-5-methoxy-1-methyl-4-nitroindole-2-carboxylate 16b

To a solution of methyl 3-ethyl-5-methoxy-1-methylindole-2-carboxylate **15b**[1] (0.354 g, 1.2 mmol) in acetic acid (3 ml), cooled to -10 °C, was added a mixture of concentrated nitric acid (0.09 ml) and acetic acid (3 ml). The mixture was stirred at room temperature for 1 h. The reaction mixture was poured in an ice/water mixture and the resulting precipitate filtered off and dried. Purification by chromatography, eluting with ethyl acetate/hexane (1:1), gave the *title compound* in (0.26 g, 62%) yield as a yellow crystalline solid, mp 131 – 133 °C (from hexane/ethyl acetate); (Found: C, 57.4; H, 5.4, N, 9.4. $C_{14}H_{16}N_2O_5$ requires C, 57.5; H, 5.5, N, 9.6 %); ν_{max} (KBr)/cm^{-1} 2974, 2953, 1707; δ_H (300 MHz; $CDCl_3$) 7.43 (1 H, d, *J* 9.2, ArH), 7.15 (1 H, d, *J* 9.2, ArH), 3.99 (3 H, s, OMe), 3.96 (3 H, s, OMe), 3.94 (3 H, s, NMe), 2.83 (2 H, q, *J* 7.4, $C\underline{H_2}Me$), 1.14 (3 H, t, *J* 7.4, $CH_2\underline{Me}$); δ_C (100 MHz; $CDCl_3$) 162.6, 145.1, 134.8, 134.2, 127.7, 123.5, 117.2, 112.8 (CH), 112.3 (CH), 58.1 (Me), 51.8 (Me), 32.4 (Me), 18.3 (CH_2), 16.2 (Me); *m/z* (CI) 315 ($M+Na^+$, 15%), 293 (MH^+, 9), 119 (100).

Methyl 4-amino-3-ethyl-5-methoxy-1-methylindole-2-carboxylate 17b

To a suspension of methyl 3-ethyl-5-methoxy-1-methyl-4-nitroindole-2-carboxylate **16b** (0.182 g, 0.62 mmol) in ethanol (30 ml) were added tin powder (0.73 g, 6.1 mmol) and hydrochloric acid (3 M; 12 ml). The mixture was stirred at room temperature for 1 h. The solution was decanted from the excess tin, neutralized with saturated aqueous sodium hydrogen carbonate, and diluted with an equal volume of water. The mixture was extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography, eluting with ethyl acetate/hexane (1:1), to yield the *title compound* as a pale yellow solid (0.16 g, 94%), mp 83 – 84 °C (from ethyl acetate/hexane); (Found: C, 64.3; H, 7.03, N, 10.4. $C_{14}H_{18}N_4O_3$ requires C, 64.1; H, 6.9, N, 10.7%); ν_{max} (KBr)/cm^{-1} 3452, 3312, 2974, 2942, 1702, 1616; δ_H (300 MHz; $CDCl_3$) 7.05 (1 H, d, *J* 8.8, ArH), 6.66 (1 H, d, *J* 8.8, ArH), 4.45 (2 H, br s, NH_2), 3.93 (3 H, s, OMe), 3.88 (6 H, s, OMe, NMe), 3.21 (2 H, q, *J* 7.6, $C\underline{H_2}Me$), 1.34 (3 H, t, *J* 7.6, $CH_2\underline{Me}$); δ_C (100 MHz; $CDCl_3$) 163.2, 139.3, 136.5, 131.2, 126.7, 124.1, 115.8, 114.0 (CH), 98.8 (CH), 58.1 (Me), 51.3 (Me), 32.1 (Me), 19.9 (CH_2), 16.8 (Me); *m/z* (EI) 263 (M^+, 100%).

5-Methoxy-1,3-dimethylindole 18

To a well stirred mixture of *N*-methyl-4-anisidine (6.00 g, 43.79 mmol) and triethylamine (16.5 ml) at 80 °C was added dropwise over 1.5 h, chloroacetone (6.24 ml, 78.83 mmol). The mixture was cooled to 25 °C, diluted with ethanol (18 ml) and followed by the addition of zinc chloride (26.28 g, 192.70 mmol). The reaction mixture was heated at 110 °C for 3 h, then quenched with ice water (78 ml) and dichloromethane (102 ml). The organic layer was separated, filtered on a pad of silica and evaporated to dryness. The crude residue obtained was purified by chromatography eluting with ethyl acetate/light petroleum (1:10), to yield the *title compound* (7.0 g, 90%) as a colourless solid, mp 56 – 57 °C (lit.,[2] mp 60 – 61 °C); ν_{max} (KBr)/cm^{-1} 2935, 2827, 1621, 1580, 1496, 1456, 1424, 1348, 1260, 1228, 1180, 1059, 1027; δ_H (300 MHz; $CDCl_3$) 7.17 (1 H, d, *J* 8.8, 7-H), 7.00 (1 H, d, *J* 2.4, 4-H), 6.89 (1 H, dd, *J* 8.8, 2.4, 6-H), 3.88 (3 H, s, OMe), 3.70 (3 H, s, NMe), 2.29 (3 H, s, Me); δ_C (100 MHz;

CDCl$_3$) 154.4, 133.3, 129.7, 128.1 (CH), 112.5 (CH), 110.7 (CH), 110.3, 101.6 (CH), 56.8 (Me), 33.5 (Me), 10.5 (Me); *m/z* (CI) 176 (MH$^+$, 100%), 161 (15), 110 (10).

5-Methoxy-1,3-dimethyl-4-nitroindole-2-carboxaldehyde 19

(a) To a solution of DMF (134 µl, 1.71 mmol) in dry dichloromethane (0.25 ml) was added dropwise phosphorus oxychloride (160 µl, 1.71 mmol) at 0 °C. The ice bath was removed. The reaction mixture was stirred for an additional 30 min and cooled in an ice bath. 5-Methoxy-1,3-dimethylindole **18** (100 mg, 0.57 mmol) in dichloromethane (0.25 ml) was added dropwise to the above solution over 15 min at 0 °C. The reaction mixture was stirred and heated to 50 °C for 1 h, poured into an ice-cold aqueous sodium hydroxide (1 M) and stirred at room temperature for another 1 h. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine until p*H* = 7, dried (Na$_2$SO$_4$), evaporated under reduced pressure. The crude product obtained was purified by chromatography eluting with ethyl acetate/light petroleum (1:3) to give *5-methoxy-1,3-dimethylindole-2-carboxaldehyde* (70.5 mg; 61%) as a light yellow crystalline solid, recrystallized from dichloromethane-pentane, mp 83 – 84 °C; (Found: C, 70.9; H, 6.4; N, 6.8. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.4; N, 6.9%); (Found: MH$^+$, 204.1024. $C_{12}H_{13}NO_2$ + H requires 204.1028); ν_{max} (KBr)/cm^{-1} 2948, 2832, 1649, 1529, 1494, 1451, 1415, 1234; δ_H (300 MHz; CDCl$_3$) 10.12 (1 H, s, CHO), 7.25 (1 H, d, *J* 9.1, 7-H), 7.10 (1 H, dd, *J* 9.1, 2.4, 6-H), 7.01 (1 H, d, *J* 2.4, 4-H), 4.03 (3 H, s, OMe), 3.88 (3 H, s, NMe), 2.61 (3 H, s, Me); nOe enhancement (3.7%) on CHO signal at δ10.12 following pre-irradiation of Me at δ2.61; δ_C (75 MHz; CDCl$_3$) 181.6 (CH), 154.7, 135.8, 132.1, 127.1, 125.8, 119.6 (CH), 111.5 (CH), 100.9 (CH), 56.0 (Me), 32.1 (Me), 8.9 (Me); *m/z* (EI) 203 (M$^+$, 100%), 188 (88), 160 (22), 131 (18), 117 (13).

(b) To a solution of indole 5-methoxy-1,3-dimethylindole-2-carboxaldehyde (2.0 g, 9.13 mmol) in acetic acid (64 ml) cooled between 0 °C and 5 °C was added a mixture of nitric acid (15.3 M; 600 µl, 9.13 mmol) and acetic acid (8 ml). The mixture was stirred at room temperature for 1 h. The mixture was poured onto ice water, extracted with dichloromethane, dried ($MgSO_4$), filtered and the filtrate evaporated under reduced pressure. The crude product was purified by chromatography eluting with ethyl acetate/light petroleum (1:3) to yield the *title compound* (1.70 g, 75%) as a yellow solid, mp 193 – 196 °C; (Found: MH^+, 248.0875. $C_{12}H_{12}N_2O_4$ + H requires 248.0874); □$_{max}$ (KBr)/cm^{-1} 3433, 2922, 1666, 1518, 1489, 1359, 1285, 1256; □$_H$ (300 MHz; $CDCl_3$) 10.18 (1 H, s, CHO), 7.44 (1 H, d, *J* 9.0, ArH), 7.23 (1 H, d, *J* 9.0, ArH), 4.04 (3 H, s, OMe), 3.95 (3 H, s, NMe), 2.46 (3 H, s, Me); □$_C$ (100 MHz; $CDCl_3$) 181.9 (CH), 145.5, 135.3, 133.8, 133.0, 121.9, 118.0, 114.3 (CH), 113.4 (CH), 58.0 (Me), 31.9 (Me), 8.1 (Me); *m/z* (CI) 248 (MH^+, 100%), 203 (60), 200 (50), 172 (35), 147 (28).

(*E*)-Ethyl 3-(5-methoxy-1,3-dimethyl-4-nitroindol-2-yl)propenoate 20

To a stirred solution of 5-methoxy-1,3-dimethyl-4-nitroindole-2-carboxaldehyde **19** (100 mg, 0.41 mmol) in dry toluene (2.5 ml) was added (ethoxycarbonylmethylene) triphenylphosphorane (154 mg, 0.45 mmol). The reaction mixture was stirred at room temperature overnight, diluted with ethyl acetate, and washed with water. The combined organic layer was dried ($MgSO_4$), filtered and the filtrate evaporated under reduced pressure. The crude material was purified by chromatography eluting with ethyl acetate/light petroleum (1:3) to yield the *title compound* (122 mg, 93%) as a yellow crystalline solid, recrystallized from dichloromethane-pentane, mp 192 – 193 °C; (Found: C, 60.0; H, 5.6; N, 8.6. $C_{16}H_{18}N_2O_5$ requires C, 60.4; H, 5.7; N, 8.8%); (Found: M^+, 318.1227. $C_{16}H_{18}N_2O_5$ requires 318.1216); □$_{max}$ (KBr)/cm^{-1} 3438, 2928, 1709, 1630, 1525, 1488, 1371, 1291, 1191, 1141, 1103, 1041; δ_H (300 MHz; CDCl$_3$) 7.76 (1 H, d, *J* 16.0, =CH), 7.32 (1 H, d, *J* 9.0, ArH), 7.01 (1 H, d, *J* 9.0, ArH), 6.29 (1 H, d, *J* 16.0, =CH), 4.28 (2 H, q, *J* 7.1, OC$\underline{H}_2$Me), 3.91 (3 H, s, NMe), 3.77 (3 H, s, OMe), 2.24 (3 H, s, Me), 1.34 (3 H, t, *J* 7.1, OCH$_2\underline{Me}$); δ_C (100 MHz; CDCl$_3$) 166.7, 145.2, 134.7, 134.6, 133.1, 131.7 (CH), 121.6 (CH), 119.3, 112.2 (CH), 111.8, 110.4 (CH), 60.9 (CH$_2$), 57.9 (Me), 31.2 (Me), 14.3 (Me), 10.1 (Me); *m/z* (EI) 318 (M$^+$, 50%), 301 (43), 288 (77), 273 (100), 270 (56), 200 (80), 168 (50).

(*E*)-3-(4-Amino-5-methoxy-1,3-dimethylindol-2-yl)prop-2-en-1-ol 21

(a) To a suspension of (*E*)-ethyl 3-(5-methoxy-1,3-dimethyl-4-nitroindol-2-yl)propenoate **20** (1.70 g, 5.60 mmol) in ethanol (94 ml) was added tin powder (3.00 g, 25.16 mmol) and hydrochloric acid (3 M; 45 ml). The mixture was stirred and heated under reflux for 1 h. Upon cooling, the reaction mixture was decanted from the excess of tin, neutralized with a saturated aqueous solution of sodium hydrogen carbonate, then diluted with an equal volume of water. The precipitate and aqueous layer were stirred overnight with dichloromethane, filtered through Celite and the layers separated. The organic layer was dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to yield (*E*)-*ethyl 3-(4-amino-5-methoxy-1,3-dimethylindol-2-yl)propenoate* (1.59 g, 98%) as an orange solid, mp 53 – 55 °C; (Found: M$^+$, 288.1475. C$_{16}$H$_{20}$N$_2$O$_3$ requires 288.1474); ν_{max} (KBr)/cm^{-1} 3467, 3314, 2979, 2906, 1701, 1613, 1520, 1497, 1459, 1286, 1174, 1047; δ_H (300 MHz; CDCl$_3$) 7.82 (1 H, d, *J* 16.1, =CH), 6.95 (1 H, d, *J* 8.8, ArH), 6.59 (1 H, d, *J* 8.8, ArH), 6.20 (1 H, d, *J* 16.1, =CH), 4.28 (2 H, q, *J* 7.1, OC$\underline{H}_2$Me), 3.86 (3 H, s, OMe), 3.70 (3 H, s, NMe), 2.68 (3 H, s, Me), 1.35 (3 H, t, *J* 7.1, OCH$_2\underline{Me}$); δ_C (100 MHz; CDCl$_3$) 167.5, 139.5, 136.4, 132.6 (CH), 131.0, 130.8, 117.5, 116.8 (CH), 116.0, 113.0 (CH), 98.5 (CH), 60.5 (CH$_2$), 58.1 (Me), 31.4 (Me), 14.4 (Me), 12.6 (Me); *m/z* (EI) 288 (M$^+$, 97%), 273 (100), 200 (50).

(b) (*E*)-Ethyl 3-(4-amino-5-methoxy-1,3-dimethylindol-2-yl)propenoate (254 mg, 0.88 mmol) was dissolved in toluene (12 ml) and cooled to -78 °C. A solution of DIBAL-H (1 M in toluene; 1.85 ml, 1.85 mmol) was added dropwise, and the stirred reaction mixture allowed to warm to room temperature over 1 h, then quenched with methanol (2 ml). The reaction mixture was extracted with ethyl acetate. The combined organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude material was purified by chromatography eluting with ethyl acetate/light petroleum (1:2) to yield the *title compound* (201 mg, 84%) as a yellow solid, mp 111 – 112 °C; (Found: M^+, 246.1371. $C_{14}H_{18}N_2O_2$ requires 246.1368); ν_{max} (KBr)/cm^{-1} 3375, 2929, 2860, 1602, 1495, 1461, 1363, 1303, 1257, 1205, 1167, 1048; δ_H (400 MHz; $CDCl_3$) 6.87 (1 H, d, *J* 8.6, ArH), 6.58 (1 H, d, *J* 8.6, ArH), 6.56 (1 H, d, *J* 16.1, =CH), 6.07 (1 H, dt, *J* 16.1, 5.5, =CH), 4.37 (2 H, d, *J* 5.5, $C\underline{H}_2OH$), 3.87 (3 H, s, OMe), 3.57 (3 H, s, NMe), 2.58 (3 H, s, Me); OH not observed; δ_C (100 MHz; $CDCl_3$) 139.6, 134.7, 133.0, 132.5 (CH), 130.1, 119.9 (CH), 117.6, 110.7 (CH), 108.5, 98.5 (CH), 64.0 (CH_2), 58.2 (Me), 30.8 (Me), 12.2 (Me); *m/z* (EI) 246 (M^+, 22%), 230 (50), 228 (70), 213 (100), 185 (30).

5-Methoxy-1,3-dimethyl-4-nitro-2-vinylindole 22

To a stirred solution of methyltriphenylphosphonium bromide (1.08 g, 3.03 mmol) in toluene (4.4 ml) at 0 °C was added dropwise *n*-butyllithium (1.6 M; 1.89 ml, 3.03 mmol). The reaction mixture was stirred at 0 °C for 10 min and at room temperature for 40 min, then added to a stirred solution of 5-methoxy-1,3-dimethyl-4-nitroindole-2-carboxaldehyde **19** (250 mg, 1.01 mmol) in dry toluene (4.4 ml) at 0 °C. The reaction mixture was stirred at room temperature for 20 min and heated at 85 °C for 30 min, cooled to 0 °C and quenched with acetone (5.5 ml). Ethyl acetate was added, the organic layers dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude material was purified by chromatography eluting with ethyl acetate/light petroleum (1:1) to yield the *title compound* (106 mg, 43%) as a yellow crystalline solid, recrystallized from dichloromethane-pentane, mp 116 – 119 °C; (Found: C, 62.9; H, 5.6; N, 11.0. $C_{13}H_{14}N_2O_3$ requires C, 63.4; H, 5.7; N, 11.4%); (Found: M H$^+$, 247.1088. $C_{13}H_{14}N_2O_3$ + H requires 247.1083); ν_{max} (KBr)/cm^{-1} 3420, 2929, 2849, 1618, 1518, 1358, 1279, 1251, 1183, 1139, 1111, 1043; δ_H (300 MHz; $CDCl_3$) 7.30 (1 H, d, *J* 8.9, ArH), 6.94 (1 H, d, *J* 8.9, ArH), 6.72 (1 H, dd, *J* 17.7, 11.7, $C\underline{H}=CH_2$), 5.66 (1 H, d, *J* 11.7, $CH=C\underline{H}H$), 5.59 (1 H, d, *J* 17.7, $CH=CH\underline{H}$), 3.93 (3 H, s, NMe), 3.71 (3 H, s, OMe), 2.19 (3 H, s, Me); δ_C (75 MHz; $CDCl_3$) 145.4, 138.9, 135.5, 134.2, 125.5 (CH), 121.6 (CH), 120.0, 111.9 (CH_2), 108.5 (CH), 106.8, 58.2 (Me), 31.0 (Me), 9.8 (Me); *m/z* (CI) 247 (MH$^+$, 62%), 217 (100), 201 (30), 186 (5), 156 (5).

4-Amino-2-ethyl-5-methoxy-1,3-dimethylindole 23

(a) To a solution of 5-methoxy-1,3-dimethyl-4-nitro-2-vinylindole **22** (29 mg, 0.12 mmol) in dry methanol (5 ml) was added palladium on carbon (10%; 10 mg) in dry methanol. The mixture was stirred overnight under a hydrogen atmosphere. The product was filtered through Celite, washed through with methanol, and finally concentrated *in vacuo*. The crude product was purified by chromatography eluting with ethyl acetate/light petroleum (1:2) to give *2-ethyl-5-methoxy-1,3-dimethyl-4-nitroindole* (15.5 mg, 53%) as a yellow solid used directly in the next step, mp 131 – 132 °C; ν_{max} (KBr)/cm^{-1} 2923, 2850, 1461, 1374; δ_H (300 MHz; $CDCl_3$) 7.26 (1 H, d, *J* 8.9, ArH), 6.86 (1 H, d, *J* 8.9, ArH), 3.91 (3 H, s, OMe), 3.66 (3 H, s, NMe), 2.75 (2 H, q, *J* 7.6, $C\underline{H}_2Me$), 2.08 (3 H, s, Me), 1.18 (3 H, t, *J* 7.6, $CH_2\underline{Me}$); δ_C (75 MHz; $CDCl_3$) 138.2, 136.2, 126.5, 123.7, 113.1, 104.4 (CH), 100.0 (CH), 96.6, 51.3 (Me), 23.0 (Me), 11.0 (Me), 7.3 (CH_2), 1.76 (Me).

(b) To a suspension of the above nitro compound (41 mg, 0.17 mmol) in ethanol (4 ml) was added tin powder (89 mg, 0.75 mmol) and hydrochloric acid (3 M; 1.1 ml). The mixture was stirred and heated under reflux for 1 h. After cooling, the reaction mixture was decanted from the excess of tin and neutralized with a saturated aqueous solution of sodium hydrogen carbonate, and then diluted with an equal volume of water. The precipitate and aqueous layer were stirred overnight with dichloromethane (10 ml), filtered through Celite and the layers separated. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to yield the *title compound* (32 mg, 89%) as a light yellow oil; (Found: MH^+, 219.1517. $C_{13}H_{18}N_2O$ + H requires 219.1497); ν_{max} (film)/cm^{-1} 2920, 2851, 1462, 1371; δ_H (300 MHz; $CDCl_3$) 6.85 (1 H, d, *J* 8.6, ArH), 6.61 (1 H, d, *J* 8.6, ArH), 3.88 (3 H, s, OMe), 3.58 (3 H, s, NMe), 2.72 (2 H, q, *J* 7.5, $C\underline{H}_2Me$), 2.52 (3 H, s, Me), 1.18 (3 H, t, *J* 7.5, $CH_2\underline{Me}$); δ_C (75 MHz; $CDCl_3$) 132.8, 130.9, 127.1, 123.0, 110.6, 102.6 (CH), 97.6, 91.5 (CH), 51.6 (Me), 22.8 (Me), 10.6 (Me), 7.7 (CH_2), 4.4 (Me); *m/z* (CI) 219 (MH^+, 100%), 113 (15).

2-[(4-Hydroxymethyl)phenoxy]methyl-5-methoxy-1,3-dimethylindole-4,7-dione 28

A solution of tetrabutylammonium fluoride (1 M in THF; 364 µl, 0.37 mmol) was added to a solution of 2-[4-(*tert*-butyldimethylsiloxymethyl)phenoxymethyl]-5-methoxy-1,3-dimethylindole-4,7-dione **27** (83 mg, 0.18 mmol) in dry THF (2.5 ml). The reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated and the residue purified by chromatography, eluting with ethyl acetate/dichloromethane (1:2) to yield the *title compound* (45 mg, 72%) as a bright orange crystalline solid; mp 154 – 157 °C; (Found: MH^+, 342.1341. $C_{19}H_{19}NO_5$ + H requires 342.1341); λ_{max} (acetonitrile)/nm 277 (log ε 4.10), 348 (3.44), 440 (3.22); ν_{max} (KBr)/cm^{-1} 3537, 3428, 2919, 2855, 1673, 1641, 1596, 1496, 1472, 1372, 1332, 1216, 1164; δ_H (300 MHz; $CDCl_3$) 7.32 (2 H, d, *J* 8.7, ArH), 6.93 (2 H, d, *J* 8.7, ArH), 5.95 (1 H, s, 6-H), 4.97 (2 H, s, OCH_2), 4.64 (2 H, s, OCH_2), 3.98 (3 H, s, NMe), 3.81 (3 H, s, OMe), 2.36 (3 H, s, Me); OH not observed; δ_C (100 MHz; $CDCl_3$) 179.5, 178.1, 160.5, 157.8, 134.7, 132.7, 130.3, 129.0 (CH), 122.3, 121.7, 115.3 (CH), 107.3 (CH), 65.0

(CH_2), 58.6 (CH_2), 56.7 (Me), 33.2 (Me), 10.4 (Me); *m/z* (ES) 359 ($M+NH_4^+$, 40%), 342 (MH^+, 95), 218 (90), 146 (20), 114 (100), 100 (50), 91 (35), 59 (60).

3-[4-(*tert*-Butyldimethylsiloxymethyl)phenoxymethyl]-5-methoxy-1,2-dimethylindole-4,7-dione 31

Diethyl azodicarboxylate (500 μl, 3.19 mmol) was added to a stirred solution of 3-hydroxymethyl-5-methoxy-1,2-dimethylindole-4,7-dione **30** (250 mg, 1.06 mmol), 4-(*tert*-butyldimethylsiloxymethyl)phenol (633 mg, 2.66 mmol) and triphenylphosphine (691 mg, 2.66 mmol) in dry THF (19 ml). The reaction mixture was stirred at room temperature overnight. The mixture was evaporated, diluted with dichloromethane, washed three times with NaOH solution (2 M), water and evaporated to dryness. The residue was purified by chromatography, eluting with ethyl acetate/dichloromethane (2:5) to give the *title compound* (202 mg, 42%) as a bright orange crystalline solid; mp 111 – 115 °C; (Found: $M+NH_4^+$, 473.2475. $C_{25}H_{33}NO_5Si + NH_4$ requires 473.2472); λ_{max} (acetonitrile)/nm 284 (log ε 4.20), 336 (3.54), 452 (3.31); ν_{max} (KBr)/cm^{-1} 3425, 2956, 2928, 2856, 1661, 1637, 1601, 1509, 1469, 1256, 1220, 1092; δ_H (400 MHz; $CDCl_3$) 7.22 (2 H, d, *J* 6.7, ArH), 6.95 (2 H, d, *J* 6.7, ArH), 5.61 (1 H, s, 6-H), 5.29 (2 H, s, OCH_2), 4.66 (2 H, s, OCH_2), 3.88 (3 H, s, NMe), 3.80 (3 H, s, OMe), 2.30 (3 H, s, Me), 0.93 (9 H, s, CMe_3), 0.09 (6 H, s, Me); δ_C (100 MHz; $CDCl_3$) 178.8, 178.2, 159.6, 157.5, 138.1, 133.8, 128.7, 127.5 (CH), 121.3, 117.4, 114.8 (CH), 106.7 (CH), 64.7 (CH_2), 60.4 (CH_2), 56.5 (Me), 32.4 (Me), 26.0 (Me), 18.4, 9.9 (Me), -5.2 (Me); *m/z* (ES) 473 ($M+NH_4^+$, 70), 430 (40), 279 (50), 123 (25), 99 (97), 91 (100).

3-[(4-Hydroxymethyl)phenoxy]methyl-5-methoxy-1,2-dimethylindole-4,7-dione 32

A solution of tetrabutylammonium fluoride (1 M in THF; 746 μl, 0.75 mmol) was added to a solution of (3-[4-(*tert*-butyldimethylsiloxymethyl)phenoxymethyl]-5-methoxy-1,2-

dimethylindole-4,7-dione **31** (170 mg, 0.37 mmol) in dry THF (5 ml). The reaction mixture was stirred at room temperature for 1.5 h. The mixture was concentrated and the residue purified by chromatography, eluting with ethyl acetate/dichloromethane (1:1) to yield the *title compound* (94 mg, 74%) as a bright orange crystalline solid; mp 174 – 176 °C; (Found: M+NH_4^+, 359.1605. $C_{19}H_{19}NO_5$ + NH_4 requires 359.1601); λ_{max} (acetonitrile)/nm 200 (log ε 3.90), 228 (3.97), 288 (3.82), 344 (2.75), 448 (2.57); ν_{max} (KBr)/cm^{-1} 3495, 2923, 2858, 1667, 1640, 1594, 1509, 1463, 1225, 1152; δ_H (400 MHz; $CDCl_3$) 7.25 (2 H, d, *J* 8.4, ArH), 6.97 (2 H, d, *J* 8.4, ArH), 5.59 (1 H, s, 6-H), 5.28 (2 H, s, OCH_2), 4.58 (2 H, s, OCH_2), 3.87 (3 H, s, NMe), 3.79 (3 H, s, OMe), 2.29 (3 H, s, Me); OH not observed; δ_C (100 MHz; $CDCl_3$) 178.7, 178.2, 159.6, 158.1, 138.1, 133.4, 128.7 (CH), 121.3, 117.1, 115.04, 115.0 (CH), 106.7 (CH), 65.0 (CH_2), 60.4 (CH_2), 56.5 (Me), 32.4 (Me), 9.9 (Me); *m/z* (ES) 364 (MNa^+, 80%), 359 (M+NH_4^+, 80), 342 (MH^+, 30), 288 (15), 242 (100), 217 (80), 42 (65).

Ethyl 3-formyl-5-methoxy-1-methylindole-2-carboxylate 35

To a solution of DMF(1 ml, 12.88 mmol) in dry dichloromethane (2 ml) was added dropwise phosphorus oxochloride (1.2 ml, 12.88 mmol) at 0 °C. The ice bath was removed. The reaction mixture was stirred for an additional 30 min and cooled in an ice bath. Ethyl 5-methoxy-1-methylindole-2-carboxylate **34**[3] (1.00 g, 4.29 mmol) was added portionwise to the above solution over 5 min at 0 °C. The reaction mixture was stirred and heated to 50 °C for 1 h, poured into an ice-cold NaOH aqueous solution (1 M) and stirred at room temperature for another 1 h. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed twice with Hydrochloric acid (2 M), water, dried over $MgSO_4$, and evaporated under reduced pressure to give the *title compound* (1.05 g, 93%) as a light yellow crystalline solid, recrystallized from dichloromethane-pentane; mp 140 – 142 °C; (Found: C, 64.2; H, 5.7; N, 5.2. $C_{14}H_{15}NO_4$ requires C, 64.4; H, 5.8; N, 5.4%);

(Found: M$^+$, 261.1007. $C_{14}H_{15}NO_4$ requires 261.1001); ν_{max} (KBr)/cm^{-1} 2992, 2903, 1716, 1639, 1511, 1480, 1413, 1247, 1214, 1137; δ_H (300 MHz; $CDCl_3$) 10.61 (1 H, s, CHO), 7.95 (1 H, d, *J* 2.5, 4-H), 7.33 (1 H, d, *J* 9.1, 7-H), 7.08 (1 H, dd, *J* 9.1, 2.5, 6-H), 4.50 (2 H, q, *J* 7.1, OC$\underline{H}_2$Me) 4.07 (3 H, s, NMe), 3.91 (3 H, s, OMe), 1.47 (3 H, t, *J* 7.1, OCH$_2\underline{Me}$); δ_C (75 MHz; $CDCl_3$) 189.0 (CH), 161.4, 157.8, 133.8, 133.5, 125.7, 119.7, 118.3 (CH), 111.8 (CH), 103.5 (CH), 62.4 (CH_2), 56.1 (Me), 33.0 (Me), 14.7 (Me); *m/z* (EI) 261 (M$^+$, 25%), 232 (100), 217 (5), 189 (5).

Ethyl 3-formyl-5-methoxy-1-methyl-4-nitroindole-2-carboxylate 36

Ethyl 3-formyl-5-methoxy-1-methylindole-2-carboxylate **35** (250 mg, 0.96 mmol) was added to concentarted nitric acid (12.5 ml) at -10 °C. The reaction mixture was stirred at -10 °C for 25 min, followed by addition of ice (50 g). The mixture was extracted with dichloromethane, dried over $MgSO_4$, filtrated and evaporated under reduced pressure. The product obtained was azeotroped twice with toluene. The crude product was purified by chromatography, eluting with ethyl acetate-light petroleum (1:1) to yield the *title compound* (271 mg, 93%) as a light yellow crystalline solid, recrystallized from dichloromethane-pentane; mp 212 – 214 °C; (Found: C, 54.2; H, 4.3; N, 9.2. $C_{14}H_{14}N_2O_6$ requires C, 54.9; H, 4.6; N, 9.1%); (Found: M$^+$, 306.0846. $C_{14}H_{14}N_2O_6$ requires 306.0852); ν_{max} (KBr)/cm^{-1} 3094, 2979, 2921, 1713, 1663, 1536, 1501, 1482, 1393, 1239, 1174, 1105, 1059; δ_H (400 MHz; $CDCl_3$) 10.40 (1 H, s, CHO), 7.55 (1 H, d, *J* 9.2, ArH), 7.25 (1 H, d, *J* 9.2, ArH), 4.53 (2 H, q, *J* 7.1, OC$\underline{H}_2$Me), 4.08 (3 H, s, NMe), 3.96 (3 H, s, OMe), 1.46 (3 H, t, *J* 7.1, OCH$_2\underline{Me}$); δ_C (100 MHz; $CDCl_3$) 185.6 (CH), 160.4, 148.2, 136.1, 133.8, 117.8, 116.2, 113.4 (CH), 112.7 (CH), 62.8 (CH_2), 57.7 (Me), 32.8 (Me), 14.2 (Me), one C unobserved; *m/z* (EI) 306 (M$^+$, 45%), 276 (82), 261 (100), 230 (82), 202 (95), 174 (50).

Ethyl 4-amino-3-formyl-5-methoxy-1-methylindole-2-carboxylate 37

To a suspension of ethyl 3-formyl-5-methoxy-1-methyl-4-nitroindole-2-carboxylate **36** (2.53 g, 8.66 mmol) in ethanol (146 ml) was added tin powder (4.66 g, 38.95 g-atom) and Hydrochloric acid (3 M; 60 ml). The mixture was stirred and heated under reflux for 1 h. Upon cooling, the reaction mixture was decanted from the excess of tin and neutralized with a saturated aqueous solution of $NaHCO_3$. The suspension obtained was added to an equal volume of water. The precipitate and aqueous layer were stirred overnight with dichloromethane, filtered through Celite and the layers separated. The organic layer was dried over Na_2SO_4 and concentrated to yield the *title compound* (2.26 g, quantitative) as a red crystalline solid, recrystallized from ethyl acetate-pentane; mp 73 – 74 °C; (Found: C, 60.8; H, 5.9; N, 10.3. $C_{14}H_{16}N_2O_4$ requires C, 60.9; H, 5.8; N, 10.1%); (Found: M^+, 276.1107. $C_{14}H_{16}N_2O_4$ requires 276.1110); $□_{max}$ (KBr)/cm^{-1} 3456, 2923, 1700, 1600, 1512, 1492, 1468, 1384, 1239, 1215, 1183; $□_H$ (400 MHz; $CDCl_3$) 10.32 (1 H, s, CHO), 7.04 (1 H, d, *J* 8.8, ArH), 6.58 (1 H, d, *J* 8.8, ArH), 6.05 (2 H, bs, NH_2), 4.50 (2 H, q, *J* 7.1, $OC\underline{H}_2Me$), 3.92 (3 H, s, NMe), 3.89 (3 H, s, OMe), 1.46 (3 H, t, *J* 7.1, $OCH_2\underline{Me}$); $□_C$ (100 MHz; $CDCl_3$) 187.6 (CH), 161.0, 141.2, 136.3, 135.7, 133.2, 121.0, 113.3 (CH), 113.1, 96.5 (CH), 62.3 (CH_2), 57.3 (Me), 32.6 (Me), 14.3 (Me); *m/z* (EI) 276 (M^+, 82%), 261 (100), 233 (57), 215 (40), 187 (16), 149 (27).

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